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(57) Abstract: The present invention is directed in part to the discovery of a novel signal transduction pathway that regulates estrogen responsiveness. Human extracellular signal-regulated kinase 8 (ERK8) has been discovered by applicants to preferentially enhance the destruction of ER α , and loss of ERK8 is correlated with breast cancer progression. Thus monitoring the expression of ERK8 can be used as a diagnostic and therapeutic indicator of cancer and cancer progression.